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FDA Updates Guidance For Investigating OOS Test Results for Pharma Production

On May 16, 2022, the FDA's Center for Drug Evaluation and Research (CDER) released Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production - Level 2 revision Guidance for Industry. The purpose of this guidance is to provide the FDA's current thinking on how to evaluate out-of-specification (OOS) test results, including the responsibilities of laboratory personnel, the laboratory phase of the investigation, additional testing that may be necessary, when to expand the investigation outside the laboratory, and the final evaluation of all test results.

The scope of this guidance includes chemistry-based laboratory testing of drugs regulated by CDER and in-house testing of drug product components that are purchased by a manufacturer and can be used by contract firms performing production and/or laboratory testing responsibilities.

The FDA defines OOS as all test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMFs), official compendia, or by the manufacturer. Additionally, OOS applies to all in-process laboratory tests that are outside of established specifications.

The FDA's initiative for current good manufacturing practices (cGMP), "Pharmaceutical CGMPs for the 21st Century," encourages modern approaches to manufacturing, monitoring, and control to enhance process predictability and efficiency using process analytical technology (PAT). PAT utilizes process controls and data as the release specification instead of relying on a single laboratory test to make batch release decisions. This guidance does not intend to address PAT approaches.

Background

There are several sections of 21 CFR 211: Current Good Manufacturing Practice for Finished Pharmaceuticals that are applicable to OOS investigations, including §211.84 Testing and approval or rejection of components, drug product containers, and closures, §211.113 Control of microbiological contamination, §211.160 General requirements, §211.165 Testing and release for distribution, and §211.194 Laboratory records. These sections address requirements for laboratory testing and validation requirements to ensure components, containers and closures, in-process materials, and finished products conform to specifications. CGMPs also apply to active pharmaceutical ingredients (APIs). API cGMPs include raw material testing, in-process monitoring, release and stability testing, process validation, and investigations of any OOS results. Manufacturers and contract testing laboratories are required and responsible for meeting these requirements.

Phase I: Laboratory Investigations

§211.192 Production record review requires a documented investigation, including the conclusions and follow-up, anytime an OOS result occurs, including rejected batches, to determine the cause of the OOS test result. The purpose of an investigation of an OOS result for a rejected batch is to determine if the OOS result is associated with other batches of the same drug product or other products.

OOS investigations should be scientifically sound, thorough, timely, unbiased, and well-documented. An OOS result can be due to an issue with measurement, with the manufacturing process, or a combination thereof. However, during the first (initial) phase of the investigation, the laboratory data should be

assessed before test preparations are discarded, so the same test preparations can be used to verify and/or eliminate laboratory error or instrument malfunctions as the OOS source. When no causative errors or clearly causative laboratory errors are identified in the analytical method used to arrive at the data, a Phase II full-scale OOS investigation should be conducted. If the OOS occurs at a contract laboratory, the laboratory should convey its data, findings, and supporting documentation to the manufacturer's quality unit (QU). When no causative errors or clearly causative laboratory errors are identified, the manufacturer's QU should initiate a Phase II full-scale OOS investigation.

The laboratory analyst should be properly trained, including training on the test methods, be aware of potential problems that could occur during the testing process, watch for problems that could create inaccurate results, and ensure that only those instruments meeting established performance specifications are used and that all instruments are properly calibrated. If the testing system is not properly functioning, the laboratory analyst should ensure any data collected during the suspect time is properly identified and is not used and the cause of the malfunction identified.

The laboratory analyst should check data for compliance with test specifications before discarding test preparations or standard preparations. When unexpected results are obtained with no apparent root cause, the laboratory analyst should inform the laboratory supervisor and an immediate assessment regarding the accuracy of the test results should be conducted. If errors are obvious (have assignable root causes), the laboratory analyst should immediately document the issue and not continue the analysis if they expect to later invalidate the results due to an assignable cause.

The laboratory supervisor should objectively assess the OOS results in a timely manner and assess the relevant data to ascertain if the results might be attributed to laboratory error or the manufacturing process.

The FDA recommends the laboratory supervisor discuss the test method with the laboratory analyst; confirm the laboratory analyst's knowledge of and performance of the test procedure; examine the raw data obtained in the analysis; identify anomalous or suspect information; verify that the calculations used to convert raw data values into a final test result are appropriate and correct; determine whether unauthorized or unvalidated changes have been made to automated calculation methods; confirm the performance of the instruments; determine that the appropriate reference standards, solvents, reagents, and other solutions were used and that they met preestablished specifications; evaluate the performance of the test method to ensure that it is performing based on method validation data and historical data; and fully document and preserve records of this laboratory assessment.

The laboratory supervisor's assignment of a root cause for OOS results is facilitated when the retained sample preparations and retained solutions are examined promptly.

The laboratory supervisor should be aware of trends regarding laboratory errors. Frequent laboratory errors suggest problems including inadequate training of laboratory analysts, poorly maintained or improperly calibrated equipment, or careless work. An increase in the frequency of laboratory errors should be a cause for concern and escalated to top management. The laboratory error rate is a typical metric discussed during management review. OOS test results should never be attributed to analytical error without completing a comprehensive investigation that clearly establishes a laboratory root cause.

Phase II: Full-Scale OOS Investigations

When laboratory error is determined not to have contributed to the OOS result, and testing results appear to be accurate, a Phase II full-scale OOS investigation should be conducted using a preestablished procedure. A Phase II full-scale investigation should include a review of production and sampling procedures, which may require additional laboratory testing and an evaluation of the OOS result(s) on distributed batches.

The QU should lead the investigation and involve all other departments that could potentially be implicated, such as manufacturing (including contracted off-site manufacturing), process development, maintenance, and engineering.

A Phase II full-scale OOS investigation should consist of a comprehensive, well-documented review. The review should include a clear statement of the reason for the investigation; a summary of the aspects of the manufacturing process that may have caused the problem; the results of a documentation review, with the assignment of actual or probable cause; the results of a review to determine if the problem has occurred previously; and a description of any corrective actions taken.

If the Phase II full-scale OOS investigation confirms the OOS result and successfully identifies the root cause, the OOS investigation may be concluded and the product rejected. If the Phase II full-scale OOS investigation extends to other batches or products that may have been associated with the specific failure, that part of the investigation must be completed prior to closure. If any materials are subsequently reprocessed, the investigation should document reprocessing and include the signatures of appropriate personnel, including production and QU personnel.

Frequent OOS results may indicate a flaw in product or process design; it is essential that redesign of the product or process be conducted to ensure reproducible product quality.

A Phase II full-scale OOS investigation may include additional laboratory testing beyond the testing performed in Phase I, including retesting a portion of the original sample and resampling.

Retesting may be useful for investigating testing instrument malfunctions or to identify a possible sample handling problem. Samples used for retesting should be taken from the same homogeneous material that was originally collected from the lot, tested, and yielded the OOS results. It may be appropriate to perform retesting using another laboratory analyst with at least the same experience and qualification as the original laboratory analyst.

Repeated “testing to compliance” is never acceptable and may result in FDA inspectional observations and/or enforcement actions.

If a Phase II full-scale OOS investigation indicates laboratory error as the root cause, the retest results are substituted for the original test result, all original data are retained, and an explanation recorded.

If a Phase II full-scale OOS investigation indicated no laboratory or calculation errors in the first test, there is no scientific basis for invalidating initial OOS results in favor of passing retest results, and all passing and suspect test results should be reported and considered in batch release decisions.

Resampling involves analyzing a specimen from additional units collected as part of the original sampling procedure or from a new sample collected from the same batch. Resampling should be performed by the

same qualified and validated methods that were used for the initial sample. When all data have been analyzed, the investigation may conclude the original sample was prepared improperly and not representative of the actual batch quality.

Reporting and interpretation of test results may include averaging and outlier tests; however, proper averaging and outlier testing methods must be utilized.

Depending upon the sample and its purpose, averaging data can yield valid results. For example, if the sample can be assumed to be homogeneous, using averages can provide a more accurate result.

When a series of complete tests, such as assays, are part of the test method, it may be appropriate to specify in the test method that the average of these multiple assays is considered one test and represents one reportable result. Averaging test data should only be used during an OOS investigation if it was used during the original testing that produced the OOS result.

Averaging may hide variability among individual test results or conceal variations in different portions of a batch or within a sample. All individual test results should be reported as separate values. Averaging the result(s) of the original test that prompted the investigation with additional retest or resample results obtained during the OOS investigation is not appropriate because it hides variability among the individual results.

An outlier is a value obtained that is markedly different from the others in a series obtained using a validated method. The reason for an outlier can be an error in the testing procedure or inherent variability in the sample being tested. A procedure for detecting and handling outliers should be developed in advance. Statically, an outlier observation can and should be omitted from calculations to prevent bias. All test results should be reported to the customer on the certificate of analysis.

Closing The Investigation

The QU is responsible for interpreting the results of OOS investigations. Initial OOS results do not mean the batch fails and must be rejected. OOS results should be investigated, and the findings of the investigation, including retest results, interpreted to evaluate the batch and reach a decision regarding release or rejection.

Where an investigation has revealed a root cause, and the suspect result is invalidated, the result should not be used to evaluate the quality of the batch or lot. When the investigation indicates an OOS result is caused by a factor affecting the batch quality, the result should be used in evaluating the quality of the batch or lot.

In cases where a series of results from multiple sample preparations from the original sample are required by the test procedure and some of the individual results are OOS, some are within specification, and all are within the known variability of the method, the passing results are no more likely to represent the true value for the sample than the OOS results. The manufacturer should err on the side of caution and treat the average of these values as an OOS result, even if that average is within specification.

If you are averaging results from the same final sample preparation, there may be cases where the test method specifies appropriate acceptance criteria for variability and a predefined number of replicates from the final diluted sample solution to arrive at a result. In these cases, and given the acceptance criteria

for variability are met, the result of any individual replicate in and of itself should not cause the reportable result to be OOS.

Borderline results that are within specification, such as an assay result that is low but within specifications, should raise a concern.
Field Alert Reports

OOS test results for products that are the subject of an approved new drug application or abbreviated new drug application are considered to be one kind of "information concerning any failure" described in §314.81 Other postmarketing reports. Regulations require submission within three working days of a field alert report (FAR) with information concerning any failure of a distributed batch to meet any of the specifications established in an application. Unless the OOS result on the distributed batch is found to be invalid within three days, an initial FAR should be submitted. A follow-up FAR should be submitted when the OOS investigation is completed.

Conclusion

This guidance highlights the importance of conducting a documented investigation, including the conclusions and follow-up, anytime an OOS result occurs, including rejected batches. The investigation should determine the root cause of the OOS test result and provide the basis for manufacturers and testing facilities to develop procedures to define the OOS process.

Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 or electronic comments to https://www.regulations.gov. Please reference docket number FDA-1998-D-0019 with all comments.

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